REMARKS

I. The Invention

The present invention relates to the surprising discovery that a broad and effective anti-tumor immunity can be achieved in a patient when inactivated tumor cells and bispecific or trispecific antibodies capable of specifically binding the tumor cells, T cells, and Fc receptor-bearing effector cells are administered separately in a time-staggered fashion, *i.e.*, the administration of tumor cells is prior to the administration of the antibodies, or *vice versa*, by a time interval ranging from 1 to 48 hours.

II. Claim Amendment

Claims 1-23 were originally filed and claims 24-38 were later added. Upon entry of the present amendment to claims 1 and 2, the limitation that the time interval is 1-48 hours is imported from claim 2 to claim 1. This amendment introduces no new matter and requires no new search. Furthermore, this amendment was not submitted earlier because Applicants did not in good faith believe that such amendment would be necessary to overcome the outstanding claim rejections. The entry of the amendment is therefore respectfully requested.

III. Claim Rejections

A. 35 U.S.C. §103

Claims 1, 4-23, and 28-38 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Berd (U.S. Patent No. 6,458,369) in view of Lindhofer *et al.* (a) (*Blood* 88:4651-4658, 1996), Lindhofer *et al.* (b) (U.S. Patent No. 6,551,592), Multihoff *et al.* (*Int. J. Cancer* 61:272-279, 2995), and Jedlitschky *et al.* (U.S. Patent No. 6,235,785). Applicants respectfully traverse the rejection, particularly in light of the present claim amendment.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to

combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

The pending claims are directed to a method for inducing a specific immunity against tumor cells by administering to a patient: (1) autologous tumor cells or allogeneic tumor cells of the same tumor type following treatment to prevent the tumor cells' survival after reinfusion; and (2) intact bispecific and/or trispecific antibodies capable of binding to a T cell, to at least one antigen on the tumor cell, and to Fc receptor-positive cells. The inactivated tumor cells and the bispecific or trispecific antibodies are administered with a time interval of 1-48 hours in between, regardless of the order in which the tumor cells and the antibodies are administered.

In contrast, the Berd reference relates to compositions comprising hapten-modified tumor cells and the use of such compositions for eliciting anti-tumor immunity in a patient. The reference describes the inactivation of the tumor cells by irradiation to prevent their revival after being administered to a patient, and also describes the co-administration of this tumor cell-containing composition with other therapeutic modalities including antibodies (column 9, lines 42-62). The manner of such co-administration is described as "together or consecutively" (column 9, line 52).

The Lindhofer (a) reference relates to the use of bispecific antibodies targeting operationally tumor-specific antigens in leukemia patients following bone marrow transplant. The Lindhofer (b) reference relates to a method for inducing an anti-tumor immunity in a patient by redirecting T cells to tumor cells via the action of a bispecific antibody , which is capable of concomitant binding of a T cell, a tumor cell, and an Fc receptor-bearing effector cell. These two references do not teach or suggest the co-administration of inactivated tumor cells and the bispecific antibodies in a patient, let alone the administration of the tumor cells and antibodies at a time interval.

The Multihoff reference reports the expression of heat shock protein (HSP) 72 and 90 on the surface of certain human tumor cells but not found on normal cells. The

Jedlitschky references relates to the use of mitomycin C as a chemtherpeutic agent. These two references thus are relevant only to the dependent claims of this application, as they do not provide the missing limitations of claim 1.

In the communication submitted on February 18, 2005, Applicants contended that not all limitations of claim 1 are provided by the cited references. More specifically, Applicants asserted that it has not been pointed out where in the cited references one might find the limitation that there should be a time interval between the administration of the inactivated tumor cells and the bispecific or trispecific antibodies, because the Berd reference used the word "consecutive[]" to describe the manner of co-administration of a tumor cell-containing composition (such as irradiated tumor cells) with other therapeutic modalities (such as antibodies), which Applicants argued that does not inherently require the presence of a time interval.

In the Final Office Action mailed May 6, 2005, the Examiner argued that, when broadly construed, Berd's "consecutive" administration could still read on the pending claims that do not specify the length of a time interval (second paragraph on page 3 of the Final Office Action). Applicants do not agree with the Examiner, because the doctrine of inherency requires the presence of a claim limitation to be a certainty and not a mere possibility. Yet, to expedite prosecution, claim 1 has been amended to recite a specific time interval of 1-48 hours. This amendment strengthens Applicants' position that all claim limitations are not provided by the cited references.

In response to Applicants' contention that the cited references teach away from administration of antibodies and tumor cells in a time staggered fashion and that the effectiveness of such time delayed co-administration is a surprising discovery, the Examiner argued that, because the Berd reference teaches administration of tumor cells to elicit an anti-tumor immune response by inducing T cells targeting the tumor cells, it would be obvious, in view of Lindhoffer (b), to administer bispecific antibodies that bind both T cells and the tumor cells after the administration of the tumor cells (the first and second paragraphs on page 4 of the

Final Office Action). Applicants again disagree with the Examiner. These references do not contain detailed discussion with regard to the order of administering tumor cells and antibodies. Only Berd mentions, in a brief sentence, that the co-administration of the inactivated tumor cells and other therapeutic agents (including antibodies) may be performed in a simultaneous or consecutive manner. This cannot be said to provide any motivation for one skilled artisan to administer the tumor cells and antibodies with any significant amount of time delay in between, let alone a specific time interval of 1-48 hours.

In summary, Applicants contend that no *prima facie* obviousness has been properly established. The withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

B. Double Patenting

Claims 1-38 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-24 of copending application USSN 10/378,218.

Applicants submit that the Examiner should withdraw the provisional double patenting rejection and allow the claims pending in the present application. According to the MPEP §822.01, "[i]f the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent..." This is precisely the case in the present application, as the only other rejection, the obviousness rejection, has been overcome in light of the present claim amendment and above discussions. On the other hand, USSN 10/378,218 has not been allowed. Thus, Applicants respectfully request that the Examiner withdraw the provisional double patenting rejection and allow the pending claims in the present application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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